의학박사 학위논문

Impacts of the introduction of DSM-5 on the epidemiological estimates of dementia and mild cognitive impairment

DSM-5 도입이 치매 및 경도인지장애 역학지표 추정에 미치는 영향

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지도교수 김 기 웅

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Impacts of the introduction of DSM-5 on the epidemiological estimates of dementia and mild cognitive impairment

by

Ji Won Han, M.D.

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Professor _____ Chairman

Professor _____ Vice Chairman

Professor _____

Professor _____

Professor _____

Abstract

Impacts of the introduction of DSM-5 on the epidemiological estimates of dementia and mild cognitive impairment

Han, Ji Won

Department of Psychiatry, College of Medicine

The Graduate School

Seoul National University

Background: To examine the impact of the revised diagnostic criteria for neurocognitive disorders (NCDs) in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 on the prevalence estimates of dementia and mild cognitive impairment (MCI).

Methods: Two independent nationwide community random samples: 755 participants aged 65 years or older from the Nationwide Survey on Dementia Epidemiology in Korea (NaSDEK) 2012 and 6,818 participants aged 60 years or older from the community-based prospective elderly cohort named Korean Longitudinal Study on Cognitive Aging and Dementia (KLOSCAD) were re-diagnosed according to the DSM-5 criteria.

Results: The estimated age-, gender-, education-, and urbanicity-standardized prevalences of major and mild NCDs (NaSDEK/KLOSCAD) were 8.35%/5.15% and 11.10%/15.99%, respectively, and those of dementia and MCI were 8.74%/ 5.32% and 27.18%/26.64%, respectively. Cohen's kappa for dementia and major

NCD was 0.988/0.969, and that for MCI and mild NCD was 0.151/0.210. Prevalence of dementia was not significantly changed according to any age, gender, and educational strata and that of MCI decreased significantly in all strata except the strata of those aged 75 years or older, females, and those with seven or more years of education.

Conclusion: Diagnostic discrepancies between major/mild NCDs and dementia/ MCI, which have mainly been due to the operationalization of neuropsychological performance criteria, may decrease in prevalence with the introduction of DSM-5. Hierarchical application of each criterion may minimize subjects with diagnostic orphans, which are caused by mismatches between neuropsychological performance and the level of functional impairment when using DSM-5.

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Keywords: prevalence, DSM-5, dementia, mild cognitive impairment, major neurocognitive disorder, mild neurocognitive disorder, epidemiology

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List of Abbreviations

AD: Alzheimer's disease

ADL: Activities of Daily Living

CDR: Clinical Dementia Rating

CERAD-K-C: Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet Clinical Assessment Battery

CERAD-K-N: Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Assessment Battery

CI: Confidence Interval

DSM: Diagnostic and Statistical Manual of Mental Disorders

DSM-5: the fifth version of the DSM

DSM-IV: the fourth version of the DSM

DST: Digit Span Test

FAB: Frontal Assessment Battery

FLAIR: FLuid Attenuated Inversion Recovery

GMS: Geriatric Mental State

IADL: Instrumental Activities of Daily Living

ICD: International Classification of Disease

IQCODE: Informant Questionnaire of Cognitive Decline in the Elderly 16-item Short Version

IWG-MCI: International Working Group on Mild Cognitive Impairment

KLOSCAD: Korean Longitudinal Study on Cognitive Aging and Dementia

MAC-Q: Memory And Cognition Questionnaire

MCI: Mild Cognitive Impairment

MINI-K: Korean version of Mini International Neuropsychiatric Interview

MMSE: Mini-Mental State Examination

MNCD: Major NeuroCognitive Disorder

mNCD: mild NneuroCognitive Disorder

NaSDEK: Nationwide Survey on Dementia Epidemiology of Korea

NCD: NeuroCognitive Disorder

PHQ-9: Patient Health Questionnaire

SD: Standard Deviation

SGDS: Short Geriatric Depression Scale

SIDAM: Structured Interview for Diagnosis of Dementia of Alzheimer type, Multi-infarct Dementia and Dementia of other Aetiology according to DSM-IIIR, DSM-IV and ICD-10

SNUBH: Seoul National University Bundang Hospital

INTRODUCTION

Epidemiological indices of dementia such as prevalence, incidence, and risk factors are considerably influenced by changes in the diagnostic criteria [1]. For example, the prevalence estimates of dementia according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV were much lower than those according to the DSM-III (13.7% versus 29.1%, respectively) [1] and slightly higher than those according to the DSM-III-R (9.6% versus 6.3%, respectively) [2].

The 5th version of DSM (DSM-5), which was released in 2013, introduced two new diagnostic categories: major neurocognitive disorder (NCD) and mild NCD. Conceptually major NCD replaced "dementia" in previous DSM versions. However, its diagnostic criteria in the DSM-5 were not similar to those of dementia in previous DSM versions [3-5]. DSM-5 did not require the presence of learning and memory impairments in diagnosing major NCD nor the presence of impairments in at least two domains [6], while it did require a substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing, in addition to subjective concerns of cognitive decline (Table 1, Appendix S1).

Mild NCD newly introduced mild cognitive impairment (MCI) into DSM as a diagnostic category. Its diagnostic criteria were quite similar to those for MCI proposed by the International Working Group on MCI (IWG-MCI) [7], except that delirium or other mental disorders should be excluded to diagnose mild NCD in DSM-5. Although DSM-5 did not recommend a specific neurocognitive assessment for diagnosing major or mild NCD, it noted that deficits on any given test would be expected to be between 1 and 2 standard deviations (SDs) below the appropriate norm for a diagnosis of mild NCD, and 2 SDs or more below the appropriate norm for a diagnosis of major NCD [6] (Table 2, Appendix S2).

Table 1. Comparison of diagnostic criteria: dementia vs. major neurocognitive disorder (NCD)

Diagnostic criteria	DSM-IV: Dementia	DSM-5: major NCD
Necessary cognitive domains of significant decline	learning and memory impairment	none
Number of cognitive domains to be evaluated	memory impairment, aphasia, apraxia, agnosia, disturbance in executive function: 5 domains	complex attention, executive function, learning and memory, language, perceptual-motor, social cognition: 6 domains
Changed cognitive domains	apraxia + agnosia	perceptual-motor complex attention (new) social cognition (new)
Necessary number of cognitive domains of decline	two or more	one or more (including amnestic disorder in DSM-IV)
Evidence from standardized neuropsychological testing	not needed	needed (2 SD or more below the norm)

Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders; SD, Standard Deviation

Table 2. Comparison of diagnostic criteria: MCI vs. mild neurocognitive disorder (NCD)

Diagnostic criteria	IWG-MCI: MCI	DSM-5: mild NCD
Cognitive domains to be evaluated	not suggested specifically	complex attention, executive function, learning and memory, language, perceptual-motor, social cognition: 6 domains (Same as major NCD)
Evidence from standardized neuropsychological testing	needed (more than 1.5 SD below the norm)	needed (between 1.0 and 2.0 SD below the norm): newly introduced lower limit for differentiating from major NCD
Comorbid major neuropsychiatric disorders	did not affect the diagnosis	excluded when they explained cognitive deficits better

Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders; IWG-MCI, International Working Group on MCI; MCI, Mild Cognitive Impairment; SD, Standard Deviation

Inevitably, these changes in both nomenclature and diagnostic criteria introduced in DSM-5 brought concerns about the comparability of the epidemiological estimates and clinical outcomes between major/mild NCD and dementia/MCI. The reduced numbers of impaired cognitive domains may increase, while the limited range of neuropsychological performance may reduce, the prevalence estimates of major NCD compared to those of dementia diagnosed according to DSM-IV diagnostic criteria. The exclusion of major mental disorders may reduce, while the limited range of neuropsychological performance may either increase or reduce the prevalence estimates of mild NCD compared to those of MCI diagnosed according to IWG-MCI diagnostic criteria.

There have been three population-based studies that investigated the impact of DSM-5 on the prevalence estimates of dementia and/or MCI (Table 3). However, these studies were subject to several methodological limitations. First, none of them investigated the impact of each criterion on the prevalence estimates separately [8-10]. Second, two of them investigated the impact on the prevalence estimates of MCI/mild NCD only, even though the prevalence estimates of MCI/mild NCD and dementia/major NCD may influence each other [9, 10]. Third, two of them did not investigate the diagnostic orphans produced by the introduction of DSM-5 [8, 9]. Fourth, one of them did not describe how they operationalized each diagnostic criterion, and thus their results cannot be directly compared to the results of other studies [9].

Objectives

This study aimed to investigate the impact of DSM-5 on the prevalence estimates of dementia and MCI simultaneously in two independent nationwide populations with the following hypotheses. (1) The reduction in the number of impaired cognitive domains for the diagnosis of major NCD, from two (including memory

function) to one (regardless of memory impairment), will increase the prevalence estimate of major NCD compared to that of dementia. (2) The increase in the number of cognitive domains to be evaluated for the diagnosis of major/mild NCD, from five to six, will increase the prevalence estimates of major NCD/mild NCD compared to those of dementia/MCI. (3) The addition of performance on standardized neuropsychological tests that is two or more SDs below age-, gender-, education-adjusted norms for the diagnosis of major NCD will decrease the prevalence estimate of major NCD compared to that of dementia. (4) The change in the performance of standardized neuropsychological tests for the diagnosis of mild NCD, from 1.5 SDs below the norm to 1-2 SD below the norm will increase the prevalence estimate of mild NCD compared to that of MCI, since the proportion below -1.5 SD corresponds to 6.7%, while -2.0 – -1.0 SD corresponds to 13.6% in a normal distribution. (5) The exclusion of major psychiatric disorder from mild NCD will decrease the prevalence estimate of mild NCD compared to that of MCI. (6) Based on hypotheses 1-3, the overall prevalence of major NCD will be decreased compared to that of dementia. Subjects with functional impairment corresponding to major NCD may already have cognitive concerns in at least two cognitive domains. The proportion of amnestic disorders or rare types of dementing illnesses may be low in community populations. Therefore, the decrease in prevalence by hypothesis 3 may surpass the increase by hypothesis 1 and 2. (7) Based on hypotheses 2, 4, and 5, the overall prevalence of mild NCD will be increased compared to that of MCI. Exclusion of major psychiatric disorder and the application of the lower limit of neuropsychological performance (2.0 SD below the norm) may decrease the prevalence of MCI. However, the increase in prevalence by hypotheses 2 and 4 may surpass the decrease by hypothesis 5. (8) Changes mentioned in hypotheses 1-7 will have different impacts on the prevalence rate according to demographic characteristics, such as age, gender, and

educational level. (9) There will be some cases that cannot be diagnosed as any NCD by DSM-5 because of the discrepancy between cognitive performance and the level of functional impairment, although they are diagnosed as MCI or dementia by DSM-IV/IWG-MCI (called diagnostic orphans).

Table 3. Previous research on the changes in prevalence produced by introduction of DSM-5

	Eramuduolla et al. [8]	Lopez-Anton et al. [9]	Luck et al. [10]
Region	Australia, Canberra (1 city), 2 Towns around Quebec	Spain, Zaragoza (5th largest city)	Germany, Leipzig
Name of Cohort	Personality & Total Health (PATH) Through Life (community-based prospective cohort)	Zaragoza Dementia and Depression (ZARADEMP) Project (community-based prospective elderly cohort), 2-phase design	Leipzig Research Center for Civilization Diseases (LIFE) (community-based cohort)
Sampling and total number of participants	Random sampling, 1,664 older people aged 72 to 78 who participated to 12 years of follow-up (baseline age: 64-64 years old)	Random sampling (Stratified extraction according to age and gender census over 55 years), 4,803 subjects	Random sampling (40-70 years old, stratified extraction according to age, gender), 1,180 older people aged 60 to 79 (one excluded by dementia, 109 excluded by partial information among 1,190)
Comparison of diagnostic criteria of dementia	DSM-IV vs. DSM-5	Not done	Not done
Comparison of diagnostic criteria of MCI	IWG-MCI [7] vs. DSM-5	Petersen MCI criteria [11] vs. DSM-5	IWG-MCI [7] vs. DSM-5
Operationalization of cognitive impairment	MNCD/mNCD/MCI: MAC-Q >24 or IQCODE >3.31 or clinician's judgement Dementia: mean Z score ≤ -2.0 SD for each domain (total 5 cognitive domains), neuropsychological battery was different from that of major NCD	Cognitive and ADL's items in the ZARADEMP Interview, Geriatric Mental State (GMS) : not describe the detailed operationalization	mNCD/MCI: structured computer-assisted interview consisted of three questionnaires about subjective memory impairment

Operationalization of neuropsychological performance	MNCD: ≤ -2.0 SD mNCD/MCI: > -2.0 to ≤ -1.0 MNCD/mNCD/MCI: using the same neuropsychological battery (6 cognitive domains) mNCD, social cognition tests were excluded for MCI	AGECAT (Automated Geriatric Examination for Computer Assisted Taxonomy), MMSE: not describe the detailed operationalization	mNCD: -2 – -1 SD MCI: ≤ -1.0 SD mNCD/MCI: using the same neuropsychological battery (6 cognitive domains including social cognition)
Operationalization of functional level	MNCD/dementia: Clinician's judgement or reported problem or Bayer IADL > 3.12 mNCD/MCI: no problem or Bayer IADL < 3.12	Lawton & Brody scale, Katz' index: detailed operationalization not described	mNCD/MCI: ≤ 1 impaired everyday activity on the SIDAM-ADL scale (MNCD: ≥ 2)
Operationalization of exclusion of major psychiatric disorder	MNCD/mNCD/dementia: PHQ-9 < 10 and clinician's judgement MCI: not excluded	detailed operationalization not described	mNCD/MNCD: SIDAM Delirium item, ≥ 23 on the CES-D, CIDI-screening questions MCI: not excluded
Study results	No information of weighted prevalence Changes of diagnosis Dementia (n = 30) to MNCD (n = 68); 127% increase MCI (n = 144) to mNCD (n = 171), 19% increase	European population adjusted weighted prevalence (age, gender stratified; January 2013) MCI 7.93% to mNCD 3.72% decrease over 65 years old	Weighted prevalence adjusted for population in Leipzig MCI (n = 237) 22.0% to mNCD (n = 222) 20.3% decrease MCI 19.5% to mNCD 20.3% increase (social cognition tests were excluded for only MCI)

Interpretation of the prevalence changes	MNCD increase: included cognitive impairment of only non-memory domains affecting functional level of dementia (n = 41), they may be non-AD dementia mNCD increase: newly diagnosed by impairment in social cognition (n = 52)	mNCD decrease: more stringent criteria for the cognitive deficit in the mNCD and by the exclusion of psychiatric disorder	mNCD decrease: exclusion of major psychiatric disorder mNCD increase (exclude social cognition for MCI): impairment of social cognition for mNCD
Diagnostic orphan when applying DSM-5	Dementia to mNCD (n = 3) MCI to Diagnostic orphan (n = 25): they could not be diagnosed to any disorders in DSM-5	Not mentioned	MCI with -2.0 SD of neuropsychological performance and functional level of non-dementia: diagnosed to mNCD (n = 30) Further mentioned the necessity of guideline for discrepancy of level of neuropsychological performance and that of functional independence. MCI to Diagnostic orphan (n = 15) due to schizophrenia or severe depression
Limitations of the study	1. Small number of research centers 2. Selection or survival bias: successful follow-up for 12 years 3. No weighted prevalence 4. Prevalence of specific age strata 3 & 4: limited generalization 5. Did not suggest a solution for diagnosis of diagnostic orphans	1. only one region 2. Small number of neuropsychological tests (n = 3) 3. Prevalence change of dementia: not performed 4. Not mentioned detailed operationalization of each criterion: the impact on the change by each criterion could not quantified.	1. only one region 2. Prevalence change of dementia: not performed

	in DSM-5 (MCI to diagnostic orphan)

Abbreviations: AD, Alzheimer's disease; ADL, Activities of Daily Living; DSM, Diagnostic and Statistical Manual of Mental Disorders; GMS, Geriatric Mental State; IADL, Instrumental ADL; IQCODE, Informant Questionnaire of Cognitive Decline in the Elderly 16-item Short Version; IWG-MCI, International Working Group on MCI; MAC-Q, Memory and Cognition Questionnaire; MCI, Mild Cognitive Impairment; MNCD, Major neurocognitive disorder; mNCD, mild neurocognitive disorder; NCD, neurocognitive disorder; PHQ-9, Patient Health Questionnaire; SD, Standard Deviation; SIDAM, Structured Interview for Diagnosis of Dementia of Alzheimer type, Multi-infarct Dementia and Dementia of other Aetiology according to DSM-IIIR, DSM-IV, and ICD-10

METHODS

This study was conducted on two independent nationwide elderly populations: the second Nationwide Survey on Dementia Epidemiology of Korea (NaSDEK) [12] and the baseline assessment of the Korean Longitudinal Study on Cognitive Aging and Dementia (KLOSCAD) [13]. In the NaSDEK, which adopted a 2-phase design (screening phase and diagnostic phase), 755 participants aged 65 years or older completed the diagnostic phase that included clinical and neuropsychological assessments. In the KLOSCAD, which adopted a 1-phase design, 6,818 participants aged 60 years or older completed clinical and neuropsychological assessments (Table 4). Owing to the limited sample size, we tested hypotheses 1, 2, 3, 4, 5, and 8 in the KLOSCAD only.

Table 4. Characteristics of the study populations

Study	NaSDEK [12]	KLOSCAD [13]
Period	Mar 2012 - Dec 2012	Nov 2010 - Oct 2012
Design	two-phase (screening & diagnostic) Cross-sectional study	Single-phase (diagnostic) Prospective longitudinal study
Sample		
Sampling	Stratified random sampling from 24 villages and towns from 16 districts across South Korea	Stratified random sampling from 30 villages and towns from 13 districts across South Korea
Size	6,008	12,496
Responders	4,016 in screening phase (67.0%) 755 in diagnostic phase (69.0%)	6,818 (53.7%)
Age	65 years or older	60 years or older
Area	Mixed (urban and rural)	Mixed (urban and rural)
Study centers	14 university hospitals and three geriatric hospitals	12 university hospitals and one geriatric hospital
Assessments	CERAD-K-C [14], CERAD-K-N [14, 15], DST [16], FAB [17], laboratory tests (dementia only), brain imaging (dementia only)	CERAD-K-C [14], CERAD-K-N [14, 15], DST [16], FAB [17], laboratory tests, brain imaging (dementia only)

Abbreviations: CERAD-K-C, Korean version of the Consortium to Establish a Registry for

Alzheimer's Disease Assessment Packet (CERAD-K) Clinical Assessment Battery; CERAD-K-N, CERAD-K Neuropsychological Assessment Battery; DST, Digit Span Test; FAB, frontal assessment battery; KLOSCAD, Korean Longitudinal Study on Cognitive Aging and Dementia; MMSE, Mini-Mental State Examination; NaSDEK, Nationwide Survey on Dementia Epidemiology in Korea; SGDS, Short Geriatric Depression Scale

Subjects (Table 5)

The NaSDEK is a multi-center, population-based, cross-sectional epidemiologic survey conducted in 2012. This study was conducted by 17 research centers (three in Seoul, four in Gyeonggi-do, one in Gangwon-do, two in Chungcheongnam-do, one in Chungcheongbuk-do, one in Jeollabuk-do, two in Gyeongsangbuk-do, two in Gyeongsangnam-do, and one in Jeju-do) and steered by the Seoul National University Bundang Hospital (SNUBH). The NaSDEK employed a two-stage design to estimate the prevalence of major NCD, mild NCD, dementia, and MCI. In the NaSDEK, 6,008 Koreans aged 65 years or older were randomly sampled from the residents of 24 villages and towns from 16 districts across South Korea, and invited to the Phase I screening assessment using the Korean version of the Mini-Mental State Examination (MMSE) [18]. Among them, 4,016 responded to the Phase I assessment (response rate = 67%), and were assigned to one of three groups according to their MMSE performance using the age-, gender-, and education-adjusted norm for elderly Koreans [17]; poor (MMSE score less than -1.5 SD from the norm), intermediate (MMSE score between -1.5 and -1.0 SD from the norm), and good (MMSE score of -1.0 SD or higher from the norm). Then, 1,097 participants (318 from the good performance group, 149 from the intermediate performance group, and 639 from the poor performance group) who were randomly sampled from each group with different group-specific sampling fractions (10% from the good performance group, 50% from the intermediate performance group, and 100% from the poor performance group), were invited to the Phase II diagnostic assessment. Among them, 755 (response rate in the good

performance group = 71%, response rate in the intermediate performance group = 77%, response rate in the poor performance group = 66%; p = 0.025) completed the Phase II diagnostic assessment (Table 5).

The KLOSCAD is a multi-center, population-based, prospective elderly cohort study launched in 2009. This study has been conducted by 13 research centers (three in Seoul, three in Gyeonggi-do, one in Gangwon-do, two in Chungcheongnam-do, one in Chungcheongbuk-do, one in Gyeongsangbuk-do, one in Gyeongsangnam-do, and one in Jeju-do) and steered by the SNUBH. In the KLOSCAD, 12,496 Koreans aged 60 years or older were randomly sampled from the residents of 30 villages and towns from 13 districts across South Korea, and 6,818 (53.7%) completed the baseline diagnostic assessment of KLOSCAD. All participants were fully informed of the study protocol, and provided written informed consent, signed by the subjects or their legal guardians. The Institutional Review Board of SNUBH (no. B-1204/149-001 for NaSDEK, no. B-0912/089-010 for KLOSCAD), Korea, approved this study protocol (no. B-1810/501-105).

Table 5. Sociodemographic and clinical characteristics of the study populations

	NaSDEK [12]	KLOSCAD [13]	P value
Participants, number	755	6,818	
Age, years (mean ± SD)	76.05 ± 7.29	70.50 ± 7.10	< 0.001
Women, number (%)	474 (62.8)	3,919 (57.5)	0.005
Education, years (mean ± SD)	6.03 ± 5.60	7.83 ± 5.38	< 0.001
Illiteracy in reading, number (%)	139 (18.4)	275 (4.0)	< 0.001
Illiteracy in writing, number (%)	145 (19.2)	323 (4.7)	< 0.001
Current occupation, number (%)	159 (21.1)	2,035 (29.8)	< 0.001
Urban residence (%)	480 (63.6)	4,851 (71.7)	< 0.001
Marital status, number (%)			
Married	434 (57.5)	4,697 (68.9)	< 0.001
Bereaved	290 (38.4)	1,789 (26.2)	
Divorced, separated, unmarried	31 (4.1)	332 (4.9)	
Cohabitants, number (%)			< 0.001
None	138 (18.3)	1,000 (14.7)	
Family	555 (74)	5,673 (83.2)	
Others	5 (0.7)	145 (2.13)	
Institutionalized	57 (7.5)	-	
Short Geriatric Depression Scale	5.79 ± 4.20	4.80 ± 3.68	< 0.001
Mini-mental State Examination	20.25 ± 6.60	25.17 ± 4.32	< 0.001

Abbreviations: KLOSCAD, Korean Longitudinal Study on Cognitive Aging and Dementia; NaSDEK, Nationwide Survey on Dementia Epidemiology in Korea; SD, standard deviation

Diagnostic assessments

In the Phase II diagnostic assessment of NaSDEK and the baseline diagnostic assessment of the KLOSCAD, geriatric psychiatrists with expertise in dementia research administered a face-to-face standardized diagnostic interview, and physical and neurological examinations to each subject using the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet

(CERAD-K) Clinical Assessment Battery (CERAD-K-C) [14]. A research neuropsychologist or trained research nurse administered the CERAD-K Neuropsychological Assessment Battery (CERAD-K-N) [14, 15], Digit Span Test (DST) [16], and frontal assessment battery [17] to each subject. Geriatric psychiatrists evaluated comorbid mental disorders, including depressive disorders, using the Korean version of the Mini International Neuropsychiatric Interview (MINI-K) [19, 20]. Computed tomography or magnetic resonance imaging (T1-weighted, T2-weighted, and fluid attenuated inversion recovery [FLAIR]) of the brain; laboratory tests, including complete blood cell counts, chemistry profiles, and a serological test for syphilis; echocardiography; and chest X-rays were conducted for each subject diagnosed with dementia to determine the subtype.

Dementia and major NCD were diagnosed according to the DSM-IV [4] and DSM-5 diagnostic criteria [21], respectively (Table 6). For a diagnosis of dementia, subjects had to exhibit memory impairment and one or more of four other cognitive disturbances (aphasia, apraxia, agnosia, and disturbance in executive functioning) that were severe enough to cause significant impairment in social or occupational functioning and to show significant decline from a previous level of functioning. Research geropsychiatrists determined the presence of functional impairment by clinical judgment and confirmed them by case conferences. We excluded major psychiatric disorder that better explained the cognitive deficits using clinicians' diagnosis of psychiatric disorders.

In contrast to the diagnosis of dementia, major NCD could be diagnosed if the subject showed evidence of cognitive decline in one or more of six cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition). The presence of cognitive concern in each domain except complex attention in DSM-5 was determined according to the previously coded information by research geropsychiatrists who directly evaluated

the participants using DSM-IV (i.e., positive cognitive concern or negative cognitive concern). To determine the presence of cognitive concern regarding complex attention, the author reviewed the previously acquired text information of cognitive concern and coded the presence of cognitive decline in complex attention. The presence of a substantial impairment in cognitive performance was ascertained by performance in one or more neuropsychological tests 2.0 SD or below the age-, gender-, and education-adjusted norm of elderly Koreans [15] as noted in the DSM-5. The threshold for impaired functional activities required for a diagnosis of major NCD was set at the same level as that for dementia, except in the case that the severity of functional decline that interferes with independence in everyday activities was indeterminate between the functional level of MCI and dementia. In that case, we classified the level of functional impairment to the level of MCI when using the IWG-MCI/DSM-IV system, but we did classify the level of functional impairment to the level of major NCD when using the DSM-5 system.

MCI and mild NCD were diagnosed according to the consensus criteria proposed by the IWG-MCI [22] and the DSM-5 diagnostic criteria [21], respectively (Table 6). Clinicians confirmed cognitive concern on the basis of careful history taking containing questioning about specific symptoms that commonly occur in individuals with cognitive deficits referring to self and/or informant reporting of cognitive decline [15]. The presence of objective cognitive impairment was ascertained by performance in one or more neuropsychological tests more than 1.5 SD below the age-, gender-, and education-adjusted norm of elderly Koreans [15]. We also applied more than 1.0 SD below the norm to maintain maximal consistency in the application of the criterion for objective impairment between the IWG-MCI and the DSM-5 in the NaSDEK. For a diagnosis of MCI, basic activities of daily living needed to be preserved, and impairment in complex instrumental functions had to be insufficient for a diagnosis

of dementia.

Similar to the criteria for major NCD, mild NCD also required evidence of cognitive decline in one or more of the six cognitive domains. However, the presence of a substantial impairment in cognitive performance was ascertained by performance in one or more neuropsychological tests within -2.0 to -1.0 SD of the age-, gender-, and education-adjusted norm of elderly Koreans as noted in the DSM-5 [23]. The threshold for impaired functional activities required for a diagnosis of mild NCD was set at the same level as that for MCI, except in the case that the severity of functional decline that interferes with independence in everyday activities was indeterminate between the functional level of MCI and dementia. In that case, we classified the level of functional impairment to the level of MCI when using IWG-MCI/DSM-IV system, but we did classify the level of functional impairment to the level of major NCD when using the DSM-5 system. We excluded major psychiatric disorder that better explained the cognitive deficits using clinicians' diagnosis of psychiatric disorders.

Table 6. Operational criteria of dementia/major neurocognitive disorder (NCD) and mild cognitive impairment (MCI)/mild NCD

Diagnostic criteria	Dementia [4]	Major NCD [21]	MCI [7]	Mild NCD [21]
A1. Cognitive concerns	≥ 2 cognitive domains including memory among the five domains: memory impairment, aphasia, apraxia, agnosia, disturbance in executive functioning; clinician's judgement using the CERAD-K-C [14]	≥ 1 cognitive domain regardless of memory impairment among the six domains: complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition; clinician's judgement using the CERAD-K-C [14]	≥ 1 cognitive domain including memory among the five domains: memory impairment, aphasia, apraxia, agnosia, disturbance in executive functioning; clinician's judgement using the CERAD-K-C [14]	≥ 1 cognitive domain regardless of memory impairment among the six domains: complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition; clinician's judgement using the CERAD-K-C [14]
A2. Impairment in neuropsychological performance	Not applicable	≤ -2.0 SDs from the norms in one or more tests*	1) < -1.5 SDs from the norms in one or more tests* 2) < -1.0 SDs from the norms in one or more tests*	-2.0 – -1.0 SDs from the norms in one or more tests*
B. Threshold of functional dependence	Clinical judgment using the CERAD-K-C [14]**		Clinical judgment using the CERAD-K-C [14],** and Not dementia/major NCD	
C. Exclude delirium or another mental disorder	Clinical judgement using the MINI-K [19, 20]**		Clinical judgement using the MINI-K [19, 20]**	

Abbreviations: CERAD-K-C, Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet (CERAD-K)

Clinical Assessment Battery; CERAD-K-N, CERAD-K Neuropsychological Assessment Battery; DST, Digit Span Test; FAB, frontal assessment battery; KLOSCAD, Korean Longitudinal Study on Cognitive Aging and Dementia; MINI-K, Korean version of Mini International Neuropsychiatric Interview; MMSE, Mini-Mental State Examination; NaSDEK, Nationwide Survey on Dementia Epidemiology in Korea; NCD, neurocognitive disorder; SD, standard deviation

[**]Confirmed by diagnostic consensus meeting

[*]Among 11 tests including 9 subtests of the CERAD-K-N [14, 15], DST [16] and FAB [17]

Statistical analysis

We compared the sociodemographic and clinical characteristics of the NaSDEK and KLOSCAD using an independent t-test for continuous variables and a chi-square test for categorical variables. For estimating prevalence of dementia, major NCD, MCI, and mild NCD, we used sample weights based on the distribution of age (60-64 years old; 65-69; 70-74; 75-79; 80-84; 85 or older), gender, educational level (0 years, 1-6 years, 7 or more years), and urbanicity (urban, rural) from the 2010 National Census data. In the NaSDEK sample, we used additional sample weights considering the sampling fractions of and response rates to Phase II diagnostic assessment. We examined the significance in the change of prevalence of dementia and MCI using paired t-tests and examined the diagnostic agreement between dementia and major NCD; for MCI and mild NCD, we used Cohen's kappa measure of agreement. To estimate the prevalence, we employed the PROC SURVEYFREQ tool in SAS version 9.3 (SAS Institute, Cary, NC), which applied Taylor's series expansion to estimate standard errors and confidence intervals (CIs). We conducted the other analyses using Statistical Package for the Social Sciences software, Release Version 22.0 (SPSS for Windows Inc., Chicago, Illinois). Two-tailed tests were used for all analyses with a value of < 0.05 considered statistically significant.

RESULTS

Prevalence estimates for dementia and major NCD (Tables 7 and 8)

In the NaSDEK sample, 505 out of 755 had cognitive concerns in one or more cognitive domains (DSM-5 A1 criterion) and 347 had concerns in two or more cognitive domains including memory (DSM-IV A criterion), indicating that the likelihood to satisfy the DSM-5 A1 criterion may be about 1.5 times higher than that to satisfy the DSM-IV A criterion. However, among the 505 participants who met the DSM-5 A1 criterion, only 388 (76.8%) had a neuropsychological performance of 2.0 SD or more below the age-, gender-, and education-adjusted norm, and thus satisfied the DSM-5 A2 criterion. Therefore, the likelihood to satisfy both the DSM-5 A1 and A2 criteria may be about 1.1 times higher than that to satisfy the DSM-IV A criterion.

Among the 388 participants who met both DSM-5 A1 and A2 criteria, 158 were functionally impaired enough to lose their independence in everyday activities and satisfied the DSM-5 B criterion. Among the 347 participants who met the DSM-IV A criterion, 161 were functionally impaired to a degree that caused significant impairment in social or occupational functioning and satisfied the DSM-IV B criterion, indicating that the likelihood to satisfy the DSM-5 A and B criteria may be comparable to that to satisfy the DSM-IV A and B criteria.

After excluding six participants who were better explained by delirium or major depressive disorder, 152 were diagnosed with major NCD according to DSM-5 diagnostic criteria and 155 were diagnosed with dementia according to the DSM-IV diagnostic criteria. The age-, gender-, education-, and urbanicity-standardized prevalences among Korean individuals aged 65 years or older was estimated to be 8.35% (95% CI = 6.39 – 10.31) for major NCD and 8.74% (95% CI = 6.70 – 10.78) for dementia; the difference between these two estimates were not statistically significant ($p = 0.898$) and Cohen's kappa between dementia and major

NCD was 0.988.

In the KLOSCAD sample, 3,356 out of 6,818 had cognitive concerns in one or more cognitive domains (DSM-5 A1 criterion) and 1,053 had concerns in two or more cognitive domains including memory (DSM-IV A criterion), indicating that the likelihood to satisfy the DSM-5 A1 criterion may be about 3.2 times higher than that to satisfy the DSM-IV A criterion. However, among the 3,356 participants who met the DSM-5 A1 criterion, only 1,614 (48.1%) had a neuropsychological performance of 2.0 SD or more below the age-, gender-, and education-adjusted norm and thus satisfied the DSM-5 A2 criterion. Therefore, the likelihood to satisfy both the DSM-5 A1 and A2 criteria may be about 1.5 times higher than that to satisfy the DSM-IV A criterion.

Among the 1,614 participants who met both DSM-5 A1 and A2 criteria, 339 were functionally impaired enough to lose their independence in everyday activities and satisfied the DSM-5 B criterion. Among the 1,053 participants who met the DSM-IV A criterion, 348 were functionally impaired to a degree that caused significant impairment in social or occupational functioning and satisfied the DSM-IV B criterion, indicating that the likelihood to satisfy the DSM-5 A and B criteria may be comparable to that to satisfy the DSM-IV A and B criteria.

After excluding six participants who were better explained by delirium or major depressive disorder, 333 were diagnosed as major NCD according to DSM-5 diagnostic criteria and 343 were diagnosed as dementia according to the DSM-IV diagnostic criteria after excluding five participants. The age-, gender-, education-, and urbanicity- standardized prevalences among Korean individuals aged 60 years or older was estimated to be 5.15% (95% CI = 4.60 – 5.70) for major NCD and 5.32% (95% CI = 4.76 – 5.88) for dementia; the difference between these two estimates were not statistically significant ($p = 0.552$) and Cohen's kappa between dementia and major NCD was 0.969.

When we analyzed each criterion separately in the KLOSCAD sample, none of the criterion changes introduced in DSM-5 produced statistically significant differences between the prevalence estimate of major NCD according to DSM-5 and that of dementia according to DSM-IV (Table 8), which was the case in all age, gender, and education strata (Table 9). In conclusion, the prevalence estimate of major NCD according to DSM-5 was found to be comparable to that of dementia according to DSM-IV in both samples.

Table 7. Diagnostic discrepancy between dementia according to the DSM-IV diagnostic criteria and major neurocognitive disorder (NCD) according to the DSM-5 diagnostic criteria in two independent elderly Korean population samples

	NaSDEK (N = 755)		KLOSCAD (N = 6,818)	
Diagnostic criteria	Dementia	Major NCD	Dementia	Major NCD
Criterion A1. Cognitive concerns				
≥ 1 cognitive domain	-	505	-	3,356
≥ 2 cognitive domains including memory	347	-	1,053	-
Criterion A2. Impairment in cognitive performance*				
All	347		1,053	
≤ -2.0 standard deviations from the standard norms	-	388	-	1,614
Criterion B. Interferes with independence in everyday activities	161	158	348	339
Criterion C. Exclude delirium or another mental disorder	155	152	343	333
Adjusted prevalence, % (95% confidence intervals)*	8.74 (6.70–10.78)	8.35 (6.39–10.31)	5.32 (4.76–5.88)	5.15 (4.60–5.70)
Cohen's kappa	0.988		0.969	

*Sample weights applied with age, gender, education, and urbanicity adjustments based on the 2010 National Census

Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders; KLOSCAD, Korean Longitudinal Study on Cognitive Aging and Dementia; NaSDEK, Nationwide Survey on Dementia Epidemiology in Korea

Table 8. Influences of the changes in each criterion introduced in DSM-5 on the difference between the prevalence[*] estimate of major neurocognitive disorder (NCD) and dementia[†] in the Korean Longitudinal Study on Cognitive Aging and Dementia (KLOSCAD) sample

	Major NCD	P value	Cohen's kappa
Criterion A1. Cognitive concerns			
A1-1. Reduced number of impaired cognitive domains	5.43 (4.86–5.99)	0.787	0.989
A1-2. Increased number of cognitive domains to be evaluated	5.32 (4.76–5.88)	1.000	1.000
Criterion A2. Impairment in cognitive performance			
Requirement of performance below -2 SD from the norms of neuropsychological tests	5.08 (4.53–5.62)	0.545	0.976
Overall	5.15 (4.60–5.70)	0.677	0.969

[*]Sample weights applied with age, gender, education, and urbanicity adjustments based on the 2010 National Census

[†]5.32 (4.76–5.88)

Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders; SD, standard deviation

Table 9. Influences of the changes in each criterion introduced in DSM-5 on the difference between the prevalence* estimate of major neurocognitive disorder (NCD) and dementia in each demographic stratum of the Korean Longitudinal Study on Cognitive Aging and Dementia (KLOSCAD) sample

Strata	Dementia	Major NCD			
		A1-1†	A1-2‡	B§	Overall
Education = 0 years					
Men					
Age < 75 years (N = 71)	6.93 (1.33–12.54)	6.93 (1.33–12.54)	6.93 (1.33–12.54)	6.93 (1.33–12.54)	6.93 (1.33–12.54)
Age ≥ 75 years (N = 77)	23.06 (13.4–32.73)	23.06 (13.4–32.73)	23.06 (13.4–32.73)	21.49 (12.16–30.83)	21.49 (12.16–30.83)
Women					
Age < 75 years (N = 449)	4.50 (2.49–6.50)	4.50 (2.49–6.50)	4.50 (2.49–6.50)	4.23 (2.29–6.17)	4.23 (2.29–6.17)
Age ≥ 75 years (N = 546)	23.41 (19.87–26.96)	23.58 (20.03–27.13)	23.41 (19.87–26.96)	22.67 (19.17–26.17)	22.84 (19.33–26.35)
Education = 1 – 6 years					
Men					
Age < 75 years (N = 503)	2.77 (1.37–4.16)	3.01 (1.54–4.48)	2.77 (1.37–4.16)	2.77 (1.37–4.16)	2.77 (1.37–4.16)
Age ≥ 75 years (N = 209)	7.25 (3.71–10.79)	7.72 (4.08–11.37)	7.25 (3.71–10.79)	6.89 (3.41–10.37)	7.37 (3.78–10.95)
Women					
Age < 75 years (N = 1,096)	1.85 (1.06–2.64)	1.85 (1.06–2.64)	1.85 (1.06–2.64)	1.85 (1.06–2.64)	1.85 (1.06–2.64)
Age ≥ 75 years (N = 468)	19.6 (17.24–21.96)	11.91 (8.69–15.12)	11.46 (8.29–14.63)	10.61 (7.56–13.67)	10.84 (7.76–13.91)

Education ≥ 7 years					
Men					
Age < 75 years (N = 1,638)	1.17 (0.65–1.68)	1.22 (0.70–1.73)	1.17 (0.65–1.68)	0.99 (0.52–1.45)	1.04 (0.56–1.51)
Age ≥ 75 years (N = 401)	7.19 (4.43–9.95)	7.19 (4.43–9.95)	7.19 (4.43–9.95)	6.93 (4.21–9.65)	6.93 (4.21–9.65)
Women					
Age < 75 years (N = 1,185)	0.90 (0.38–1.41)	0.90 (0.38–1.41)	0.90 (0.38–1.41)	0.83 (0.33–1.33)	0.83 (0.33–1.33)
Age ≥ 75 years (N = 175)	5.30 (1.81–8.80)	6.11 (2.31–9.92)	5.30 (1.81–8.80)	5.30 (1.81–8.80)	6.11 (2.31–9.92)

*Sample weights applied with age, gender, education, and urbanicity adjustments based on the 2010 National Census

[†]Reduction in the number of impaired cognitive domains for the diagnosis of major NCD

[‡]Increase in the number of cognitive domains to be evaluated for the diagnosis

[§]Addition of performance on standardized neuropsychological tests that is two or more standard deviations below age-, gender-, education- adjusted norms for the diagnosis

Prevalence estimates for MCI and mild NCD (Tables 10 and 11)

In the NaSDEK sample, 505 out of 755 had cognitive concerns in one or more cognitive domains (DSM-5 and IWG-MCI A1 criterion), 78 (15.4%) had a neuropsychological performance within -2.0 to -1.0 SD of the age-, gender-, and education-adjusted norm (DSM-5 A2 criterion). Among the 78 subjects who met the A1 and A2 diagnostic criteria, 75 subjects did not have impairment that interfered with their capacity for independence in everyday activities (DSM-5 B criterion). Among the 441 participants who met the IWG-MCI A1 and A2 diagnostic criteria, 281 had preserved or minimally impaired functional abilities and satisfied the IWG-MCI B criterion, indicating that the likelihood to satisfy the DSM-5 A and B criteria may be about 0.3 times lower than that to satisfy the IWG-MCI A and B criteria.

After the exclusion of two subjects who were better explained by delirium or major depressive disorder, 73 were diagnosed as mild NCD according to DSM-5 diagnostic criteria and 281 who met the IWG-MCI A and B criteria were diagnosed as MCI according to the IWG-MCI diagnostic criteria. The age-, gender-, education-, and urbanicity- standardized prevalences among Korean individuals aged 65 years or older was estimated to be 11.10% (95% CI = 7.74–14.46) for mild NCD and 27.18% (95% CI = 22.79–31.56) for MCI; the difference between these two estimates was statistically significant ($p < 0.001$) and Cohen's kappa between mild NCD and MCI was 0.151.

In the KLOSCAD sample, 3,356 out of 6,818 had cognitive concerns in one or more cognitive domains among five domains (DSM-5 A1 criterion) and 3,346 had cognitive concerns in one or more cognitive domains among six domains (IWG-MCI A1 criterion), indicating that the likelihood to satisfy the DSM-5 A1 criterion may be comparable to that to satisfy the IWG-MCI A1 criterion. Among the 3,356 participants who met the DSM-5 A1 criterion, only 1,156 (34.4%) had a

neuropsychological performance within -2.0 to -1.0 SD of the age-, gender-, and education-adjusted norm and thus satisfy the DSM-5 A2 criterion. On the contrary, among the 3,346 participants who met the IWG-MCI A1 criterion, 2,184 (65.3%) had a neuropsychological performance below -1.5 SD from the norm and thus satisfied the IWG-MCI A2 criterion. Therefore, the likelihood to satisfy both the DSM-5 A1 and A2 criteria may be about 0.53 times lower than that to satisfy the IWG-MCI A1 and A2 criteria.

Among the 1,156 participants who met both DSM-5 A1 and A2 criteria, 1,139 did not have impairment that interferes with their capacity for independence in everyday activities (DSM-5 B criterion). Among the 2,184 participants who met the IWG-MCI A1 and A2 diagnostic criteria, 1,838 had preserved or minimally impaired functional abilities and satisfied the IWG-MCI B criterion, indicating that the likelihood to satisfy the DSM-5 A and B criteria may be about 0.62 times lower than that to satisfy the IWG-MCI A and B criteria.

After excluding 35 participants who were better explained by delirium or major depressive disorder, 1,104 were diagnosed as mild NCD according to DSM-5 diagnostic criteria and 1,838 who met the IWG-MCI A and B criteria were diagnosed as MCI according to the IWG-MCI diagnostic criteria. The age-, gender-, education-, and urbanicity- standardized prevalences among Korean individuals aged 60 years or older was estimated to be 15.99% (15.10–16.88) for mild NCD and 26.64% (25.55–27.72) for MCI; the difference between these two estimates were statistically significant ($p < 0.001$) and Cohen's kappa between mild NCD and MCI was 0.210.

When we analyzed each criterion separately in the KLOSCAD sample, the change in criterion for the neuropsychological performance introduced in DSM-5 produced statistically significant differences between the prevalence estimate of mild NCD according to DSM-5 and that of MCI according to the IWG-MCI (Table

11), which was the case in all age, gender, and education strata except the strata of education ≥ 7 years, female, age ≥ 75 years old (Table 12). In conclusion, the prevalence estimate of mild NCD according to DSM-5 was found to be significantly lower than that of MCI according to the IWG-MCI in both the samples.

Table 10. Diagnostic discrepancy between mild cognitive impairment according to the IWG-MCI diagnostic criteria and mild neurocognitive disorder (NCD) according to the DSM-5 diagnostic criteria in two independent elderly Korean population samples

	NaSDEK (N = 755)			KLOSCAD (N = 6,818)	
Diagnostic criteria	MCI	MCI-II	Mild NCD	MCI	Mild NCD
Criterion A1. Cognitive concerns in one or more cognitive domains	505	505	505	3,346	3,356
Criterion A2. Impairment in cognitive performance					
< -1.5 standard deviations from standard norms	441	-	-	2,184	-
< -1.0 standard deviations from standard norms (II)	-	466	-		
Between -2.0 and -1.0 SDs from standard norms	-	-	78	-	1,156
Criterion B. Independence in everyday activities	281	305	75	1,838	1,139
Criterion C. Exclude delirium or another mental disorder		-	73	-	1,104
Criterion. Not normal, not dementia	281	305	-	1,838	1,104
Adjusted prevalence, % (95% confidence interval)*	27.18 (22.79–31.56)	31.85 (27.08–36.63)	11.10 (7.74–14.46)	26.64 (25.55–27.72)	15.99 (15.10–16.88)
Cohen's kappa between MCI and mild NCD	0.151	0.273		0.210	

*Sample weights applied with age, gender, education, and urbanicity adjustments based on the 2010 National Census

Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders; IWG-MCI, International Working Group on Mild Cognitive Impairment; KLOSCAD, Korean Longitudinal Study on Cognitive Aging and Dementia; NaSDEK, Nationwide Survey on Dementia Epidemiology in Korea; SD, standard deviation

Table 11. Influences of the changes in each criterion introduced in DSM-5 on the difference between the prevalence[*] estimate of mild neurocognitive disorder (NCD) and mild cognitive impairment[†] in the Korean Longitudinal Study on Cognitive Aging and Dementia (KLOSCAD) sample

	Mild NCD	P value	Cohen's kappa
Criterion A1. Cognitive concerns			
A1-2. Increased number of cognitive domains to be evaluated	26.77 (25.69–27.85)	0.864	0.996
Criterion A2. Impairment in cognitive performance			
Change in performance on standardized neuropsychological tests to 1–2 SD below the norm	16.45 (15.55–17.35)	<0.001	0.217
Criterion C. Exclusion of delirium or another mental disorder			
Addition of criterion for exclusion of delirium or another mental disorder	25.81 (24.74–26.88)	0.290	0.979
Overall	15.99 (15.10–16.88)	<0.001	0.210

[*]Sample weights applied with age, gender, education, and urbanicity adjustments based on the 2010 National Census

[†]26.64 (25.55–27.72)

Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders; SD, standard deviation

Table 12. Influences of the changes in each criterion introduced in DSM-5 on the difference between the prevalence[*] estimate of mild neurocognitive disorder (NCD) and mild cognitive impairment (MCI) in each demographic stratum of Korean Longitudinal Study on Cognitive Aging and Dementia (KLOSCAD) sample

Strata	Mild cognitive impairment	Mild NCD			
		A1-2[†]	B[‡]	C[§]	Overall
Education = 0 years					
Men					
Age < 75 years (N = 71)	36.89 (24.33–49.45)	36.89 (24.33–49.45)	4.43 (0.00–8.87)[***]	35.90 (23.42–48.38)	4.43 (0.00–8.87)[***]
Age ≥ 75 years (N = 77)	36.02 (23.45–48.59)	36.02 (23.45–48.59)	19.55 (10.45–28.64)[***]	36.02 (23.45–48.59)	19.55 (10.45–28.64)[***]
Women					
Age < 75 years (N = 449)	29.68 (25.39–33.98)	29.68 (25.39–33.98)	17.50 (13.97–21.02)[***]	28.31 (24.07–32.55)	16.91 (13.42–20.39)[***]
Age ≥ 75 years (N = 546)	37.98 (33.85–42.11)	37.98 (33.85–42.11)	11.50 (8.74–14.26)[***]	36.27 (32.18–40.36)	10.89 (8.20–13.58)[***]
Education = 1 - 6 years					
Men					
Age < 75 years (N = 503)	28.25 (24.28–32.22)	28.25 (24.28–32.22)	17.85 (14.49–21.21)[***]	27.88 (23.92–31.83)	17.24 (13.93–20.55)[***]
Age ≥ 75 years (N = 209)	36.34 (29.70–42.98)	36.34 (29.70–42.98)	21.50 (15.78–27.21)[***]	34.88 (28.31–41.46)	21.02 (15.35–26.69)[***]
Women					
Age < 75 years (N = 1,096)	26.26 (23.64–28.87)	26.34 (23.73–28.96)	20.05 (17.67–22.42)[***]	25.64 (23.05–28.23)	19.60 (17.24–21.96)[***]
Age ≥ 75 years (N = 468)	35.68 (31.27–40.10)	35.68 (31.27–40.10)	18.42 (14.86–21.99)[***]	34.42 (30.05–38.79)	17.47 (13.99–20.96)[***]

Education ≥ 7 years					
Men					
Age < 75 years (N = 1,638)	16.99 (15.15–18.82)	17.22 (15.37–19.07)	14.19 (12.46–15.92)**	16.62 (14.80–18.44)	13.95 (12.23–15.66)**
Age ≥ 75 years (N = 401)	37.07 (32.20–41.93)	37.55 (32.67–42.43)	16.98 (13.28–20.68)***	36.77 (31.91–41.62)	17.24 (13.51–20.97)***
Women					
Age < 75 years (N = 1,185)	22.81 (20.41–25.21)	23.10 (20.68–25.51)	16.51 (14.34–18.67)***	21.67 (19.31–24.03)	15.81 (13.68–17.94)***
Age ≥ 75 years (N = 175)	22.07 (15.70–28.43)	22.07 (15.70–28.43)	15.80 (9.76–21.84)	21.37 (15.09–27.65)	15.80 (9.76–21.84)

*Sample weights applied with age, gender, education, and urbanicity adjustments based on the 2010 National Census

***p<0.01, **p<0.05, *p<0.1 Compared with prevalence of MCI

†Increase in the number of cognitive domains to be evaluated for the diagnosis

‡Change in performance on standardized neuropsychological tests to 1–2 SD below the norm

§Addition of criterion for exclusion of delirium or another mental disorder

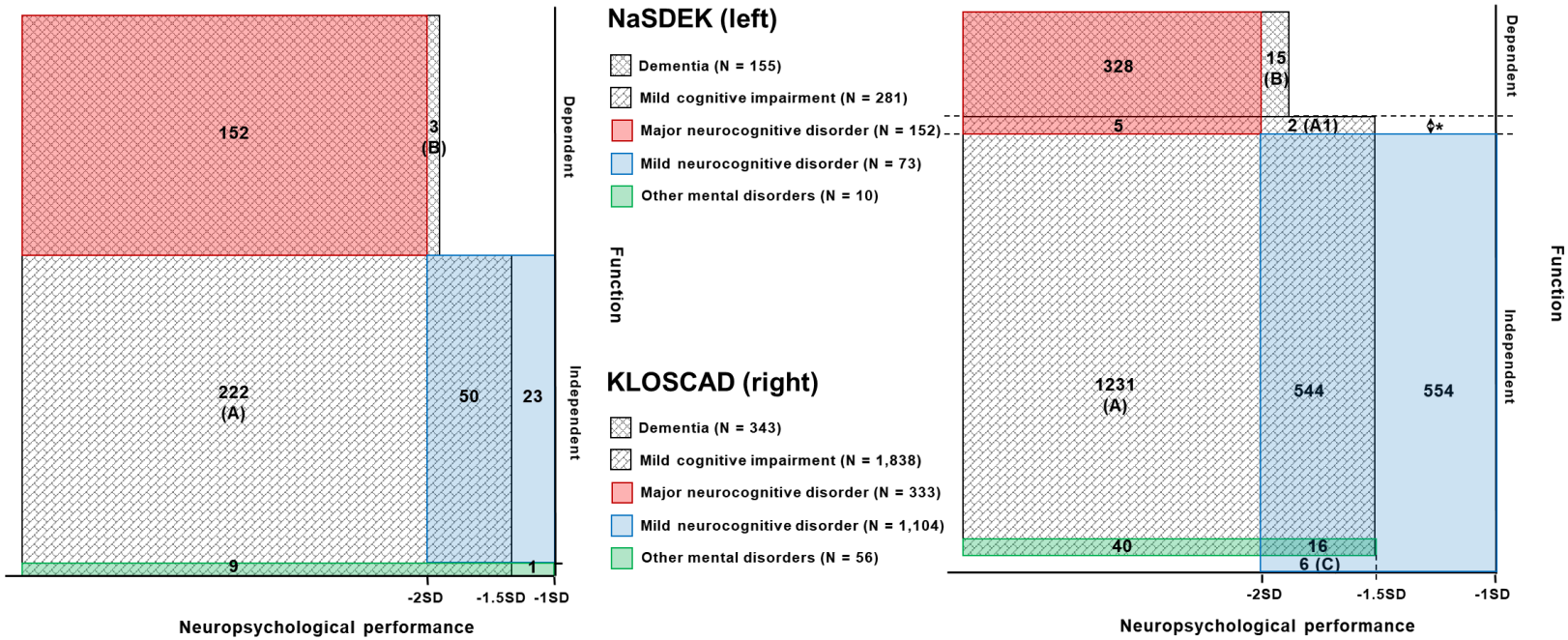
Diagnostic orphans

In NaSDEK and KLOSCAD, there were three and fifteen discrepant subjects, respectively, who were diagnosed with dementia according to the DSM-IV diagnostic criteria but not diagnosed with major NCD according to the DSM-5 diagnostic criteria. They could not be diagnosed with any NCDs (diagnostic orphans) in the DSM-5 diagnostic classification, since their neuropsychological performances were better than 2.0 SD below the standard norms; however, their functional impairments were severe enough for them to lose their independence in everyday activities (B in NaSDEK and KLOSCAD, Figure 1). On the contrary, five subjects who were diagnosed with MCI according to the IWG-MCI diagnostic criteria changed their diagnosis to major NCD in KLOSCAD (Figure 1). They could not be diagnosed with dementia because of the number of cognitive concerns being only one (three subjects with memory impairment, two subjects with executive dysfunction), with indeterminate functional impairment between MCI and dementia using the DSM-IV/IWG-MCI diagnostic system. Using the DSM-5 diagnostic system, they could be classified as having major NCD because of interference with capacity for independence in everyday activities.

In the NaSDEK, among the 281 subjects who were diagnosed with MCI according to the IWG-MCI diagnostic criteria, 231 (82.2%) were not diagnosed with mild NCD according to the DSM-5 diagnostic criteria. Among them, nine (3.9%) were better explained by other mental disorders (major depressive disorder or delirium) while 222 (96.1%) were considered diagnostic orphans in the DSM-5 diagnostic classification, since their neuropsychological performances were 2.0 or more SD worse than the standard norms but their cognitive impairment did not interfere with their capacity for independence in everyday activities ((A) in NaSDEK, Figure 1). In the KLOSCAD, among the 1,838 subjects who were diagnosed with MCI according to the IWG diagnostic criteria, 1,294 (70.4%) were

not diagnosed with mild NCD according to the DSM-5 diagnostic criteria. Among them, five (0.4%) subjects were diagnosed with major NCD, as mentioned above. Two subjects (0.2%) lost the diagnosis of MCI because they had indeterminate functional impairment between MCI and dementia but were judged to have some interference with independent functional ability ((A1) in KLOSCAD, Figure 1). Fifty-six (4.3%) subjects were better explained by major depressive disorder or schizophrenia, while 1,231 (95.1%) were considered diagnostic orphans in the DSM-5 diagnostic classification, since their neuropsychological performances were 2.0 or more SD or worse than the standard norms but their cognitive impairment did not interfere with their capacity for independence in everyday activities ((A) in KLOSCAD, Figure 1). In conclusion, the introduction of DSM-5 produced diagnostic orphans because of the discrepancy between cognitive performance and the level of functional impairment in both samples. The diagnostic orphans in (A) in KLOSCAD showed a higher conversion rate to dementia (by DSM-IV) or major NCD (by DSM-5) than the subjects with mild NCD at baseline for the six years of follow-up (Table 13).

Fig. 1. Comparison of cognitive disorders classified by the 5th Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria with those by the 4th Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and the International Working Group on Mild Cognitive Impairment diagnostic criteria



Note. Numbers indicate the numbers of subjects included in each diagnostic category.
(A) Subjects with diagnostic orphans in the DSM-5 diagnostic classification whose neuropsychological performances were 2.0 SD or more below the standard norm, but with functional independence; (A1) Subjects with diagnostic orphans whose neuropsychological

performance were within the range of mild neurocognitive disorder but whose functional impairment was regarded as showing a level of interference with independence in activities of daily living in the DSM-5 diagnostic classification; (B) Subjects with diagnostic orphans in the DSM-5 diagnostic classification whose neuropsychological performances were between -2.0 SD and -1.0 SD from the standard norm, but with loss of functional independence; (C) Subjects newly diagnosed with mild neurocognitive disorder in the DSM-5 because of cognitive concern in the complex attention domain only; *Subjects with cognitive concern in only one domain and who had indeterminate functional impairment between mild cognitive impairment and dementia but showed interference with independent daily living.

Table 13. Comparison of clinicodemographic characteristics and conversion rates to dementia between diagnostic orphans and subjects with mild neurocognitive disorder (NCD) in the KLOSCAD sample

	Diagnostic orphan (A) in Figure 1	mild NCD	p value*
Total number	1,231	1,104	
Baseline			
Age, years (mean ± SD)	72.73 ± 7.17	70.33 ± 6.53	<0.001
Women, number (%)	751 (61.0%)	648 (58.7%)	0.255
Education, years (mean ± SD)	6.28 ± 4.99	7.75 ± 5.07	<0.001
Clinical Dementia Rating, Sum of Boxes (mean ± SD)	0.73 ± 0.65	0.51 ± 0.49	<0.001
Short Geriatric Depression Scale (mean ± SD)	5.74 ± 3.64	5.30 ± 3.57	0.004
Mini-mental State Examination (mean ± SD)	23.30 ± 4.25	25.53 ± 3.01	<0.001
Two-year follow-up (n)	883	862	
Major NCD, number (%)	52 (5.9%)	16 (1.9%)	<0.001
Dementia, number (%)	55 (6.2%)	18 (2.1%)	<0.001
Four-year follow-up (n)	707	713	
Major NCD, number (%)	92 (13.0%)	28 (3.9%)	<0.001
Dementia, number (%)	99 (14.0%)	32 (4.5%)	<0.001
Six-year follow-up (n)			
Major NCD, number (%)	123 (20.5%)	42 (7.1%)	<0.001
Dementia, number (%)	125 (20.8%)	45 (7.6%)	<0.001

*p value for Chi-square test (categorical variables) or student's t-test (continuous variables)
SD, standard deviation

DISCUSSION

We estimated the prevalence of major NCD and mild NCD and compared them with those of MCI and dementia in two independent nationwide populations in Korea. The prevalence estimate of major NCD according to the DSM-5 diagnostic criteria (8.35% in NaSDEK, 5.15% in KLOSCAD) was quite comparable to that of dementia according to the DSM-IV diagnostic criteria (8.74% in NaSDEK, 5.32% in KLOSCAD; Table 7), whereas the prevalence estimate of mild NCD according to the DSM-5 diagnostic criteria (11.10% in NaSDEK, 15.99% in KLOSCAD) was significantly lower than that of MCI according to the IWG diagnostic criteria (27.18% in NaSDEK, 26.64% in KLOSCAD; Table 10). These results indicate that the introduction of the DSM-5 may have differentially influenced the prevalence estimates of dementia and MCI.

Prevalence estimates for dementia and major NCD

In the NaSDEK, there were no subjects who were significantly impaired in only one cognitive domain or impaired in two or more cognitive domains with preserved learning and memory among those who had functional impairments with sufficient severity to lose their independence in everyday activities. In the KLOSCAD, five subjects who were significantly impaired in only one cognitive domain (3 subjects with memory impairment, 2 subjects with executive dysfunction) with functional impairment of sufficient severity to lose their independence in everyday activities were newly diagnosed as major NCD (Figure 1). There were no or few subjects with cognitive impairment in only one domain sufficient to bother the independent daily activities in both samples since amnestic disorders and/or rare types of dementing illnesses are less prevalent in randomly sampled community populations than in clinical populations. No adequate studies have been conducted on the prevalence estimates of amnestic disorders [24]. The prevalence estimates of

dementia with Lewy bodies/Parkinson's disease and frontotemporal dementia were 0.11% (95% CI = 0.00–0.23) and 0.03% (95% CI = 0.00–0.08), respectively, in a representative nationwide community sample of Koreans aged 65 years or older [25]. On the other hand, a previous study performed in a memory clinic reported that about 19% of patients with MCI were reclassified as having major NCD because of the presence of impairment in only a single cognitive domain and a lack of memory impairment in 30% of patients [26]. We may question whether cognitive impairment in only one domain that has sufficient severity to cause the loss of independence in everyday activities is possible in real. In cases of the very-early phase of Alzheimer's dementia (AD), memory impairment is related to executive function [27]. In cases of non-AD, for example, major frontotemporal NCD, cognitive concerns regarding complex attention, executive function, and social cognition can be presented simultaneously, even in the early-phase.

The DSM-5 notes that a neuropsychological performance two or more SDs below the appropriate norm is a typical cutoff for ascertaining the presence of cognitive impairment [21]. Although this criterion has resulted in a minimal decrease without statistical significance in prevalence estimates of major NCD compared to that of dementia (Table 8, 9), the occurrence of diagnostic orphans due to the criterion for neuropsychological performance may be inevitable ((B) in Figure 1).

Prevalence estimates for MCI and mild NCD

In the NaSDEK, no subjects were newly defined to have cognitive concern according to the increase in the number of cognitive domains to be evaluated from five to six. In the KLOSCAD, 10 subjects were newly defined to have cognitive concern in the complex attention domain. The addition of the social cognition domain to be evaluated for diagnosing NCDs did not make any change because

subjects with impairment in social cognition also showed disturbances in executive function. As a result, an increased number of cognitive domains to be evaluated did not significantly affect the change in prevalence (Table 11).

With respect to MCI, impairments on neurocognitive testing have usually been defined as performance below 1.5 SD of the age-, gender-, and education-adjusted normative mean in a standardized test [28]. Recent attempts at early detection of at-risk individuals for dementia have divided MCI into early and late categories based on neuropsychological performance, where between 1.0 and 1.5 SD below the norm represents early MCI and more than 1.5 SD below the norm represents late MCI [28, 29]. The DSM-5 might tend to apply both early and late MCI to mild NCD. Theoretically, below -1.5 SD corresponds to 6.7% of the population with a normal distribution and -2.0 – -1.0 SD corresponds to 13.6% of the population. Thus, it might be expected to increase the prevalence of MCI. However, the change in performance on standardized neuropsychological tests from -1.5 SD to -2.0 – -1.0 SD reduced the prevalence of MCI significantly, resulting in a decrease in overall prevalence of MCI (Table 11). This may be due to the relatively small proportion of cognitive concern (37.2%) from subjects with neuropsychological performance between 1.0 SD and 1.5 SD below the norm compared with 64.4% and 71.1% from those who are between 2.0 SD and 1.5 SD, and those 2.0 SD or lower below the norms, respectively, in the KLOSCAD. The other explanation is that the relatively large proportion of subjects with neuropsychological performance of 2.0 SD or below the norm had an independent functional level in activities of daily living. Those subjects became diagnostic orphans because of the discrepancy between the levels of neuropsychological performance and functional independence ((A) in Figure 1). In the NaSDEK, using 1.0 SD below the norm for MCI increased the value of Cohen's kappa from 0.151 to 0.273 and it increased the prevalence of MCI from 27.18% to 31.85%, which

seems a natural consequence of the inclusion of early MCI without exclusion of subjects with neuropsychological performance of -2.0 SD or worse. Exclusion of delirium or major psychiatric disorder also decreased the number of subjects with MCI in the NaSDEK and KLOSCAD (Table 10), but it did not cause a significant decrease in the prevalence estimate (Table 11).

Since a majority of previous epidemiological studies have been performed on subjects with late MCI without the lower limit on neuropsychological performance, direct comparisons between the prevalence estimates of MCI and mild NCD should be conducted with caution. The prevalence of mild NCD in a Spanish elderly population was estimated to be 3.72% [9], which was only about one third or fourth of our estimate in a Korean elderly population (11.0% in NaSDEK, 15.99% in KLOSCAD). However, this difference may be largely attributed to methodological differences between the studies rather than geographical differences. For example, the prevalence estimates of MCI increased as the number of applied neuropsychological tests for objectively ascertaining the presence of cognitive impairment increased [30]. Eleven neuropsychological tests were applied in the current study whereas only three tests were applied in the study on the Spanish population by Lopez et al. [9].

Diagnostic orphans due to the discrepancy between neurocognitive performance and the level of functional independence

When we apply both criteria for neuropsychological performance and the level of functional independence for diagnosing major or mild NCDs, subjects with diagnostic orphans become inevitable because the cutoff for diagnosing either NCD using neuropsychological performance does not exactly match up with the cutoff for the functional level. Subjects with older age and extremely low or high educational attainment may raise the probability of discrepancies between

objective neuropsychological performance and functional impairment related to cognitive decline. It is possible that they may be outliers with respect to the current standard norm or their functional impairment may be over- or under-estimated. Despite this interpretation, the clinical implication of the diagnostic orphans may be the loss of at-risk clinical populations. We found that the diagnostic orphans (A) in the KLOSCAD (Figure 1) had a higher conversion rate to major NCD than those who were diagnosed with mild NCD, at two-, four-, and six-year follow-ups (Table 13). After adjusting variables that showed significant differences between diagnostic orphans and subjects with mild NCD, diagnostic orphans were associated with about a 2.0-fold risk for progression to major NCD at two-, four-, and six-year follow-ups.

To solve the problem of diagnostic orphans, we recommend against operating on the lower limit of the typical range of neuropsychological performance (-2.0 SD) for diagnosing mild NCD and the upper limit of the typical range of neuropsychological performance (-2.0 SD) for diagnosing major NCD. Accordingly, diagnostic orphans such as (A) in Figure 1 could be mild NCDs and diagnostic orphans such as (B)(A1) in Figure 1 could be major NCDs. We can also give hierarchical priority to one of the two criteria for neuropsychological performance and functional impairment when a diagnostic orphan occurs. Giving priority to the former may increase the prevalence estimate of major NCD and giving priority to the latter may minimize the diagnostic discrepancy between DSM-IV/IWG-MCI and DSM-5. Depending on the purpose of the diagnosis, the application of the priority may be different.

Limitations and Strengths

This study has several limitations. First, we did not conduct a standardized neuropsychological test to ascertain the presence of social cognition impairments

because the current study was conducted prior to the release of the DSM-5. This may have reduced the diagnostic discrepancy between major/mild NCD and dementia/MCI. Second, although we gathered comprehensive and detailed data that included history, neurological and physical examinations, comprehensive neuropsychological tests, and laboratory and neuroimaging tests using the CERAD-K Assessment Battery, NCD diagnoses were made by retrofitting the dataset of the NASDEK and KLOSCAD, which was conducted before the release of the DSM-5. Third, we did not employ instruments for activities of daily living. However, we determined functional impairment by the stringent clinical judgment of a research geropsychiatrist, and corroborated the judgment through case conferences with four research geropsychiatrists.

The strengths of the present study were that it was the first study to investigate the impact of each changed criterion in the DSM-5 on the prevalence of dementia and MCI. Moreover, we investigated the differential impact of each changed criterion according to demographic characteristics. Results may have generalizability because the same results from two independent representative random samples were found despite the differences in the sociodemographic and clinical characteristics between the two samples. Finally, it is the first study to examine the impact of the introduction of DSM-5 on the prevalence of dementia and MCI in an Asian population.

CONCLUSION

In conclusion, the diagnostic classifications and criteria for major NCD and mild NCD in the DSM-5 may result in a decrease in prevalence estimates from dementia/MCI to major/mild NCD. The diagnostic discrepancy was modest between major NCD and dementia, and was significant between mild NCD and MCI. Criterion about performance of standardized neuropsychological testing was

significantly attributable to a decrease in the prevalence of MCI. Hierarchical application of each criterion may minimize the number of subjects with diagnostic orphans who occurred because of a mismatch between neuropsychological performance and the level of functional impairment when using DSM-5.

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APPENDIX

S1. Diagnostic criteria for dementia and major neurocognitive disorder (NCD)

DSM-IV (1994): Dementia	DSM-5 (2013): Major NCD
A. The development of multiple cognitive deficits manifested by both: 1. Memory impairment (impaired ability to learn new information or to recall previously learned information) 2. One or more of the following cognitive disturbances: (a) aphasia (language disturbance) (b) apraxia (impaired ability to carry out motor activities despite intact motor function) (c) agnosia (failure to recognize or identify objects despite intact sensory function) (d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)	A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on: A1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and A2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.
B. The cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.	B. The cognitive deficits interfere with independence in everyday activities (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living such as pay bills or managing medications).
C. The deficits do not occur exclusively during the course of a delirium	C. The cognitive deficits do not occur exclusively in the context of a delirium The cognitive deficits are not better explained by another mental disorders (e.g., major depressive disorder, schizophrenia)

Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders

S2. Diagnostic criteria for mild cognitive impairment and mild neurocognitive disorder (NCD)

IWG-MCI (2004): Mild cognitive impairment	DSM-5 (2013): Mild NCD
International working group on MCI (2004) General criteria for MCI Not normal, not demented (Dose not meet criteria (DSM-IV, ICD-10) for a dementia syndrome) A. Cognitive decline A1. Self and/or informant report and impairment on objective cognitive tasks and/or A2. Evidence of decline over time on objective cognitive tasks B. Preserved basic activities of daily living / minimal in complex instrumental functions Original criteria (1999) for amnestic mild cognitive impairment 1. Memory complaint, preferably corroborated by an informant 2. Impaired memory function for age and education 3. Preserved general cognitive function 4. Intact activities of daily living 5. Not demented	A. Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on A1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and A2. A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment. B. The cognitive deficits do not interfere with capacity for independence in everyday activities (i.e., complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required). C. The cognitive deficits do not occur exclusively in the context of a delirium. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia)

Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders; IWG-MCI, International Working Group on MCI; MCI, Mild Cognitive Impairment

요약 (국문초록)

서론: 2013년 정신질환 진단 및 통계 편람(Diagnostic and Statistical Manual of Mental Disorders) 5판(DSM-5)에서 주요신경인지장애 및 경도신경인지장애의 진단 기준이 발표되었다. 본 연구에서는 정신질환 진단 및 통계 편람 5판의 신경인지장애 진단 기준이 치매와 경도인지장애의 유병율에 미치는 영향을 검증하고자 하였다.

방법: 두 개의 독립적인 전국단위 노인 표본인 제2차 전국치매역학조사 (Nationwide Survey on Dementia Epidemiology in Korea; NaSDEK 2012)의 진단 평가에 참여한 65세 이상 755명, 전국단위 지역사회 전향적 코호트 연구인 한국인의 인지노화와 치매에 대한 전향적 연구 (Korean Longitudinal Study on Cognitive Aging and Dementia; KLOSCAD) 기저평가에 참여한 60세 이상 6,818명의 평가 자료를 DSM-5 진단 기준에 따라 재진단하였다.

결과: 2010년 센서스 노인 인구의 연령, 성별, 교육연한, 도농 표준화 주요신경인지장애 유병율은 8.35%/5.15% (NaSDEK/KLOSCAD) 였고, 경도신경인지장애 유병율은 11.10%/15.99% 였다. DSM-IV 진단 기준에 따른 치매 유병율은 8.74%/5.32% 였고, International working group on mild cognitive impairment 진단 기준에 따른 경도인지장애 유병율은 27.18%/26.64% 였다. 주요신경인지장애와 치매의 Cohen’s kappa 값은 0.988/0.969 였으며, 경도신경인지장애와 경도인지장애의 Cohen’s kappa 값은 0.151/0.210 으로 나타났다. 신경인지검사 수행수준에 대한 진단기준 항목이 주요/경도신경인지장애와 치매/경도인지장애의 진단 불일치의 주된 요인으로 작용하였다. 연령, 성별, 교육연한 계층별 치매 유병율은 각 계층별 주요신경인지장애 유병율과 유의한 차이가 없었으나, 75세 이상, 여성, 교육연한 7년 이상인 층을 제외한 전

계층에서 경도신경인지장애 유병율은 경도인지장애 유병율에 비해 유의한 감소를 보였다.

결론: DSM-5 진단 기준을 사용할 경우 치매와 주요신경인지장애의 유병율 수준은 비슷하나, 경도인지장애에 비해 경도신경인지장애의 유병율은 유의하게 낮아진다. 신경인지검사 수행수준에 대한 진단기준항목과 일상 생활 기능에서의 독립 수준에 대한 진단기준항목 불일치에서 발생하는 진단 상실자(diagnostic orphans)를 최소화하기 위하여 진단 기준의 위계적 적용이 도움이 될 수 있다.

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주요어: 유병율, 정신질환 진단 및 통계 편람 5판, 치매, 경도인지장애, 주요신경인지장애, 경도신경인지장애, 역학

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